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(54) **PROCESS FOR PREPARATION OF DRONEDARONE BY GRIGNARD REACTION**

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C07C 233/65 (2006.01)
C07C 231/02 (2006.01)
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(52) **U.S. Cl.**
CPC ***C07D 307/80*** (2013.01); ***C07C 231/02*** (2013.01); ***C07C 233/65*** (2013.01); ***C07D 307/79*** (2013.01)

(58) **Field of Classification Search**
CPC C07D 307/80
USPC 549/67
See application file for complete search history.

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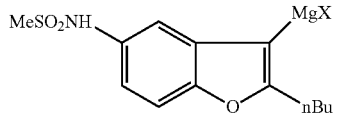
(57) **ABSTRACT**

The invention relates to a novel process for the preparation of dronedarone (I) and pharmaceutically acceptable salts thereof, which comprises reacting of compound of formula (IV) with compound of formula (VI) in a Grignard reaction, and the obtained product is isolated and, if desired, converted into a pharmaceutically acceptable salt thereof. The invention also relates to some novel intermediary compounds and processes for the preparation thereof.

(IV)



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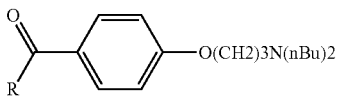

17 Claims, No Drawings

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U.S. Appl. No. 14/377,484, filed Aug. 7, 2014, by Huszar et al.

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PROCESS FOR PREPARATION OF DRONEDARONE BY GRIGNARD REACTION

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a National Phase application under 35 U.S.C. §371 of International Application No. PCT/EP2013/001520 filed May 23, 2013 and claims the benefit of EP Application No. 12462010.5 filed May 31, 2012, the disclosures of which are incorporated herein by reference in their entirety.

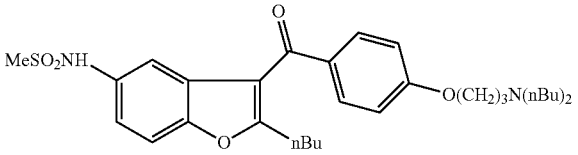
FIELD OF THE INVENTION

The invention relates to a novel process for the preparation of dronedarone and pharmaceutically acceptable salts thereof, to novel intermediary compounds used in this process and their preparation.

TECHNICAL BACKGROUND

Dronedarone, i.e. N-[2-n-butyl-3-[4-[3-(di-n-butylamino) propoxy]benzoyl]-1-benzofuran-5-yl]-methanesulfonamide, having the formula (I):

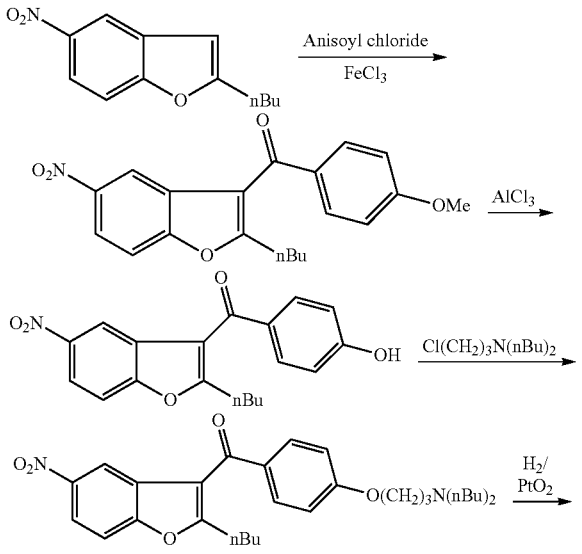
(I)



is a known drug for the treatment of arrhythmia (EP0471609).

There are some known processes for the preparation of dronedarone as follows:

In EP 0471609 the following scheme is disclosed for the preparation of dronedarone [Process A]



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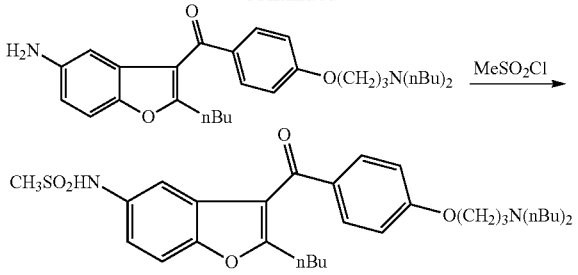
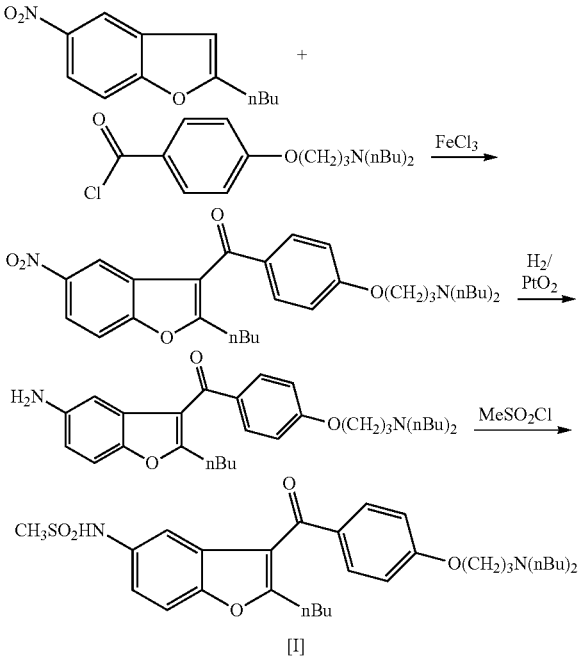


[I]

The above mentioned patent description discloses some new intermediary compounds, too.

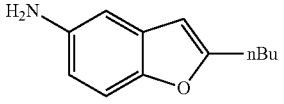
In WO 02/48078 the following scheme is disclosed for the preparation of dronedarone [Process B]:



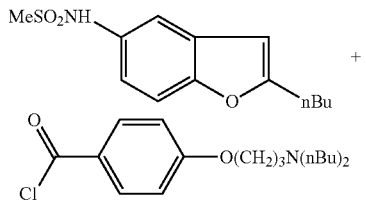
[I]

The novelty of the process is based on the adaptation of the Friedel-Crafts reaction in the first step. The process and the intermediary compounds used for the preparation of the benzoylchloride compound of the first step are also disclosed in this document. The further steps of the process are identical with the final steps of the synthetic route disclosed in EP 0471609 [Process A], but in the claims the whole synthetic route is claimed, up to dronedarone.

In WO 02/48132 (Sanofi) the following reaction route is disclosed [Process C]. This method is the so called superconvergent route. In the first step of it 5-amino-2-butyl-benzofuran



is mesylated and the obtained 2-butyl-5-methanesulfonamido-benzofuran (in HCl salt form) is further reacted in the next step as follows:



In this process the order of reaction steps are altered, the reduction and the methansulfonylation steps are performed at the beginning part of the procedure. Besides the reaction route for preparation of dronedarone, the starting material 2-butyl-5-methansulfonamido-benzofuran and its preparation are also claimed.

From among the mentioned procedures the first one [Process A] is the so called linear synthesis. In this way of procedure the different parts of the dronedarone are stepwise built up on the starting compound. This method is the least economical because the continuous step by step building of the chemical groups is performed on more and more complicated and expensive molecules, which raises the costs of the preparation.

Furthermore it comprises complicated and harmful reaction steps because aluminium chloride is used in the cleaving reaction of the methoxy group which makes the industrial feasibility more complicated.

In WO 02/48078 (Process B) a shorter synthetic route is disclosed which makes this process more economical, but its last reaction step remained the methansulfonylation reaction of the amino group. This reaction step (see the method described in example 6 of of WO 02/48078) is complicated and gives a low yield of only 61.6%. Pure product can be expected after purification using chromatographic column purification, which method is necessary because of the separation difficulties of the bis-methanesulfonylated product.

The process disclosed in WO 02/48132 (process C) is simpler and more economical taking into consideration the number of the reaction steps. Unfortunately, in the last reaction step rather impure dronedarone.HCl (hydrochloride salt) is formed which is the obvious consequence of the presence of the dibutylamino group in the Friedel-Crafts reaction. According to Examples 3 and 4, the crude dronedarone hydrochloride salt is prepared with a yield of 90% which is further purified and finally the crude dronedarone base is produced with a yield of 86%. This base is reacted with hydrogen chloride gas dissolved in isopropanol which results in pure dronedarone hydrochloride salt. No yield is given for this reaction step. According to example 5 crude dronedarone hydrochloride salt is prepared with a yield of 90%, which is washed with water and reacted with hydrogen chloride gas dissolved in isopropanol, resulting dronedarone hydrochloride salt again. The quality of this product is not known. However, since neither the components used in the Friedel-Crafts reaction nor the resulting products and by-products are soluble in water, the washing step with water cannot result any purification apart from the removal of inorganic salts.

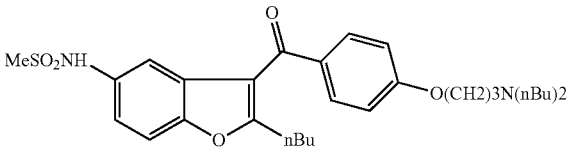
There is another drawback of this process, namely, a dimesylated side-product is formed in the mesylation reaction of the 5-amino-2-butyl-benzofuran. The purification is carried out by crystallization which has a yield of 78.5%.

It is an object of the present invention to provide a novel process for the preparation of dronedarone (I), starting from known and commercially available materials, applying simple, environmentally compatible reagents and solvents, to afford high overall yields and good purity of the product.

SUMMARY OF THE INVENTION

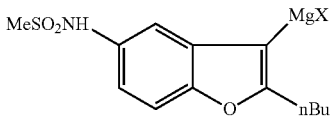
The main aspect of the invention is a process for preparation of dronedarone (I) and pharmaceutically acceptable salts thereof

[I]



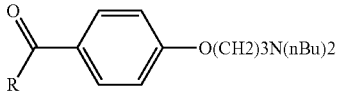
which comprises reacting of compound of formula (IV)

[IV]



with compound of formula (VI)

[VI]



in a Grignard reaction,

isolating the obtained product as a base and, if desired converting it into a pharmaceutically acceptable salt.

The idea of the process is based on the superconvergent synthesis of dronedarone (I) (WO Patent No. 02/48132), but compounds (II) and (V) are coupled with a Grignard reaction. The process is simple, its advantage compared to the previously mentioned [A] and [B] processes is that the Friedel-Crafts acylation of 2-butyl-5-nitrobenzofuran can be avoided.

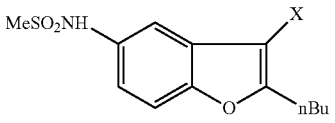
Further aspects of the invention include the compounds of formula (III), (IV) and (VI) as a new compounds, and processes for the preparation thereof (see below in the "Detailed description of the invention" part).

DETAILED DESCRIPTION OF THE INVENTION

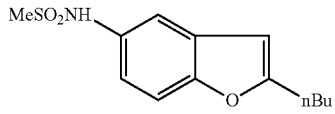
Therefore the present invention relates to a process for the preparation of dronedarone and pharmaceutically acceptable salts thereof. The whole process—starting from compounds available from commercial sources—reads as follows:

(a) a compound of formula (II) (N-(2-butyl-1-benzofuran-5-yl)methanesulfonamide) is halogenated to obtain a compound of formula (III):

[III]



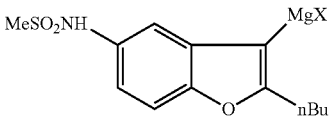
[II]



wherein X is Cl or Br;

(b) the compound of formula (III) obtained in step (a) above is converted by reacting with Mg into a compound of formula (IV):

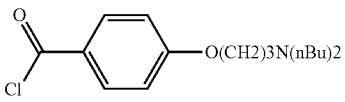
[IV]



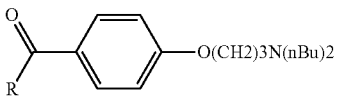
wherein X is Cl or Br; compound (IV) is not isolated in the process;

(c) a compound of formula (V) (4-(3-dibutylaminopropoxyl)benzoyl chloride) is reacted with an amine of formula R—H or its salt to obtain a compound of formula (VI):

[V]



[VI]



wherein R is a group of formula —NR^1R^2, wherein R^1 and R^2 are independently selected from H, alkyl, alkyloxy and aryl;

(d) the compound of formula (IV) is reacted with a compound of formula (VI) in a Grignard reaction to obtain dronedarone (I),

and the obtained product is isolated and, if desired, converted into a pharmaceutically acceptable salt thereof.

The intermediates (III), (IV) and (VI) are new compounds, intermediates (III) and (VI) are isolated in stable, pure form. The Grignard reagent of formula (IV), wherein X is Cl or Br, is preparable by reacting a compound of formula (III), wherein X is Cl or Br, with Mg in an anhydrous solvent. As the Grignard reagent is rather sensitive to moisture and oxygen, it is typically not isolated. It is used in the form of an anhydrous, typically ethereal solution.

Said compounds and their preparation processes [i.e. the above steps (a), (b) and (c)] form further objects of the invention.

Compounds of formula (II) and (V) are known from WO 02/48132 (Sanofi).

The reaction of step (a) is typically carried out in a solvent or in a mixture of solvents. The solvent in this step is typically selected from the group of nitriles, ketones or chlorinated solvents and any mixtures thereof. Specific examples include, among others, the mixture of dichloromethane and acetonirtile.

Either organic or inorganic halogenating agents may be used in the halogenations reaction. Typical reagents are N-bromosuccinimide, N-chlorosuccinimide or phosphoroxychloride.

The reaction is typically carried out under cooling, the temperature is typically between −10 and 0° C.

In step (b) the compound of formula (III) is converted to a compound of formula (IV), i.e. to a so-called Grignard reagent by a reaction with Mg. Typically Mg turnings are used.

The reaction is carried out in an anhydrous solvent, typically in ethers, e.g. in tetrahydrofurane (THF), 2- or 3-methyltetrahydrofurane (MeTHF), 1,4-dioxane or diethyl-ether. Usually THF is used. The reaction is typically carried out at an elevated temperature, e.g. under reflux.

The Grinard reagent of formula (IV) is not isolated, it is used in the form of the obtained solution in the Grignard reaction of step (d).

In step (c) a compound of formula (V) is reacted with an amine or a salt thereof. The amine is ammonia or an alkyl, alkyloxy or aryl amine as defined above. Specific examples are ammonia (in form of aqueous solution), dimethylamine HCl, diethylamine, aniline and N,O-dimethyl hydroxylamine HCl.

The reaction in step (c) is typically carried out in a solvent, such as halogenated, especially chlorinated solvents and aliphatic hydrocarbons. Specific examples are dichloromethane, chloroform or n-hexane.

In this step a catalyst, usually a base is used. Specific examples are pyrimidine, K_2CO_3 and trimethylsilyl chloride (TMSCl).

Due to the fast chemical reaction cooling of the reaction mixture may be beneficial before adding the catalyst. Afterwards, the reaction is usually carried out at a higher temperature, typically between room temperature and reflux temperature.

Step (d) is a Grignard reaction. Suitable reaction conditions are well known in the art (for a review see e.g. Smith, M. B.; March, J. March's Advanced Organic Chemistry, (6th ed.) Wiley, NY, 2007, and references cited therein).

The reaction is carried out in an anhydrous solvent, typically in ethers, e.g. in THF, MeTHF, 1,4-dioxane or diethyl-ether. Usually THF is used.

The reaction is typically carried out in an oxygen-free environment, e.g. under nitrogen or argon atmosphere.

In order to facilitate the reaction a catalyst, such as $FeCl_3$, $NiCl_2$, LiCl, $CuCl_2$ or iron or lithium complex catalysts may be used. A typical catalyst is $FeCl_3$.

In this reaction the temperature is chosen according to the general practice of a person skilled in organic chemistry. Typically the temperature is between 0° C. and reflux temperature, especially room temperature between 15 and 25° C.

Applicable temperature values for each step can be found in the examples.

Each reaction step is generally carried out under atmospheric pressure.

In the processes for the preparation of the intermediary compounds of formula (III) and (VI) the product is typically isolated as a base. If desired, the isolated base can be converted into a salt (acid addition salt) thereof, which is typically a pharmaceutically acceptable salt (possible acids are mentioned below). Theoretically the acid addition salt can be prepared directly if the relating acid is in the final reaction mixture from which the solid product is made (however, this way is not applied in case of these compounds where the base type form has practical importance).

The applicable acid for the preparation of pharmaceutically acceptable salts can be any inorganic or organic acid which forms an acid addition salt with the compound of general formula (I) and (VI). Exemplary acids which can form an acid addition salt are as follows: acetic acid, adipic acid, alginic acid, ascorbic acid, aspartic acid, benzoic acid, benzenesulfonic acid, boric acid, butyric acid, citric acid, ethanesulfonic acid, fumaric acid, hydrogen chloride, hydrogen bromide, hydrogen iodide, 2-hydroxyethanesulfonic acid, maleic acid, oxalic acid, methanesulfonic acid, nitric acid, salicylic acid, tartaric acid, sulfuric acid (forming sulfate or bisulfate anion), sulfonic acid (such as those mentioned herein), succinic acid, toluenesulfonic acid and the like. The hydrogen halogenide salts are typical, especially the hydrogen chloride salt.

Here it is mentioned that on the mesylate group of compounds of general formula (I) and (III) (see the "left side" of the molecules) a salt formation can be carried out (on the amide part of it) by a strong base, e.g. an alkaline hydroxide, typically by sodium hydroxide. However, these salts have less practical importance, but they are within the scope of salts. It means that the phrase "salts" embraces both the acid addition salts and the salts formed by bases (basic salts) in case of compounds of formula (I).

As used herein, the term alkyl includes straight or branched aliphatic hydrocarbon chains of 1 to 6 carbon atoms, e.g., methyl, ethyl, isopropyl and t-butyl.

As used herein, the term "alkoxy" includes alkyl-O— groups. Non-limiting examples of suitable alkoxy groups include methoxy, ethoxy, n-propoxy, isopropoxy and n-butoxy.

As used herein, the term "aryl" includes aromatic monocyclic or polycyclic ring systems comprising 6 to about 14 carbon atoms, preferably 6 to about 10 carbon atoms. Non-limiting examples of suitable aryl groups include phenyl and naphthyl.

The following non-limiting examples further illustrate the invention.

In the examples the following HPLC method was applied for the determination of the purity of the reaction products:

Column: Waters Symmetry C18 4.6×150 mm, 5 μm

Mobile phases:

Mobile phase A: 5 mM sodium phosphate buffer, pH=2.2

Mobile phase B: acetonitrile

Mobile phase C: methanol

Column temp: 25° C.

Auto sampler temp: 20° C.

Gradient:

Time (min)	A (%)	B (%)	C (%)
0	65	30	5
20	40	50	10
45	15	75	10
47	65	30	5
57	65	30	5

Injection vol: 10

Flow rate: 1.5 mL/min

Run time: 57 min

Detection: 245 nm

EXAMPLES

Example 1

N-(2-butyl-3-chloro-1-benzofuran-5-yl)methanesulfonamide (IIIa)

5.34 g (0.02 mol) of N-(2-butyl-1-benzofuran-5-yl)methanesulfonamide (II) is dissolved in 60 mL of dichloromethane and 60 mL of acetonitrile is added to the solution. 5.34 g (0.04 mol, 2 eq) of N-chlorosuccinimide in solid form is added dropwise at −8±2° C. in 20 min. The reaction mixture is stirred for 2 hours at this temperature and then heated up to 20° C. The reaction mixture is poured into 200 mL of water. The product is extracted with 2×80 mL of dichloromethane. The organic layer is evaporated and the residue is purified by column chromatography (spheric silica; eluent: toluene: methanol=7:3) to give 4.59 g (76%) of the title compound (IIIa) as a yellowish-brown solid.

Purity by HPLC: 99.4%.

Mp: 149-152° C.

^{1}H NMR ($CDCl_3$): 7.41 (d, J=2.2 Hz, 1H); 7.35 (d, J=8.5 Hz, 1H); 7.10 (dd, J=8.6 and 2.2 Hz, 1H); 6.71 (s, NH); 2.90 (s, 3H); 2.76 (t, J=7.2 Hz, 2H); 1.71 (m, 2H); 1.41 (m, 2H); 0.92 (t, J=7.1 Hz, 3H).

Example 2

N-(2-butyl-3-bromo-1-benzofuran-5-yl)methanesulfonamide (IIIb)

5.34 g (0.02 mol) of N-(2-butyl-1-benzofuran-5-yl)methanesulfonamide (II) is dissolved in 60 mL of dichloromethane and 5.34 g (0.03 mol, 1.5 eq) of N-bromosuccinimide in 60 mL of acetonitrile is added dropwise at −8±2° C. in 30 min. The reaction mixture is stirred for 3 hours at this temperature and then is poured into 150 mL of water. The product is extracted with 2×60 mL of dichloromethane. The organic layer is evaporated and the residue is purified by column chromatography (spheric silica; eluent: toluene: methanol=7:3) to give 4.89 g (71%) of the title compound (IIIb) as an orange solid.

Purity by HPLC: 99.1%.

Mp: 161-164° C.

^{1}H NMR ($CDCl_3$): 7.41 (d, J=2.2 Hz, 1H); 7.37 (d, J=8.5 Hz, 1H); 7.09 (dd, J=8.6 and 2.2 Hz, 1H); 6.71 (s, NH); 2.90 (s, 3H); 2.76 (t, J=7.2 Hz, 2H); 1.71 (m, 2H); 1.40 (m, 2H); 0.95 (t, J=7.1 Hz, 3H).

Example 3

N-(2-butyl-3-magnesium-chloro-1-benzofuran-5-yl) methanesulfonamide (IVa)

To a dried flask 0.92 g Mg turnings (0.04 mol) are placed and then a solution of 2.4 g of N-(2-butyl-3-chloro-1-benzo-

furan-5-yl)methanesulfonamide (IIIa) (0.008 mol) in 12 mL of THF is added at room temperature in 15 min. The mixture is heated slowly until the reaction starts (35-38° C.) then 9.6 g of (IIIa) (0.032 mol) in 48 mL THF is added to the reaction mixture in 40 min. During the addition the temperature of the reaction mixture reaches the reflux temperature (58-60° C.). After the addition the reaction mixture is stirred for 2 hours at reflux temperature until the solid Mg turnings disappear from the solution. The reaction mixture is cooled down to room temperature and is used in the Grignard reaction without further preparation.

Conversion by HPLC: 100%.

Example 4

N-(2-butyl-3-magne sium-bromo-1-benzofuran-5-yl) methane sulfonamide (IVb)

To a dried flask 0.92 g Mg turnings (0.04 mol) are placed and then a solution of 2.76 g of N-(2-butyl-3-bromo-1-benzofuran-5-yl)methanesulfonamide (IIIb) (0.008 mol) in 15 mL of THF is added at room temperature in 15 min. The mixture is heated slowly until the reaction starts (32-35° C.) then 11.04 g of (IIIb) (0.032 mol) in 55 mL THF is added to the reaction mixture in 45 min. During the addition the temperature of the reaction mixture reaches the reflux temperature (60-62° C.). After the addition the reaction mixture is stirred for 2 hours at reflux temperature until the solid Mg turnings disappear from the solution. The reaction mixture is cooled down to room temperature and is used in the Grignard reaction without further preparation.

Conversion by HPLC: 100%.

Example 5

4-(3-dibutylaminopropoxyl)benzamide (VIa)

6.5 g of 4-(3-dibutylaminopropoxyl)benzoyl chloride (V) (0.02 mol) is dissolved in 60 mL of n-hexane. 2.50 g of ammonium hydroxide (0.02 mol, 1 eq) and 2.76 g of potassium carbonate (0.02 mol, 1 eq) are added. The reaction mixture is heated to 50° C. and stirred for 3 hours. After the reaction the solid inorganic salt is filtered, washed with 2×5 mL of n-hexane and the filtrate is concentrated. The residue is purified by column chromatography (spheric silica; eluent: toluene:MTBE:methanol=5:4:1) to give 5.34 g of the title compound (VIa) (87%) as a yellowish solid.

Purity by HPLC: 97.9%.

M.p.: 121-123° C.

^{1}H NMR (DMSO): 7.91 (d, J=8.6 Hz, 2H); 7.7 (br, 1H); 6.86 (d, J=8.6 Hz, 2H); 4.04 (t, J=7.0 Hz, 2H); 2.56 (t, J=7.0 Hz, 2H); 2.39 (t, J=7.0 Hz, 4H); 1.87 (m, 2H); 1.33 (m, 8H); 0.86 (t, J=7.0 Hz, 6H).

Example 6

4-(3-dibutylaminopropoxy)-N,N-dimethyl-benzamide (VIb)

6.5 g of 4-(3-dibutylaminopropoxyl)benzoyl chloride (V) (0.02 mol) is dissolved in 60 mL of dichloromethane. 1.63 g of dimethylamine HCl (0.02 mol, 1 eq) is added and the reaction mixture is cooled to 0° C. 0.43 g TMSCl (0.004 mol, 0.2 eq) is added in 5 min. The reaction mixture is heated to room temperature and stirred for 5 hours. 50 mL of water is added to the mixture, it is stirred for 15 min and the phases are separated. The organic phase is washed with 30 mL of water then it is concentrated. The residue is purified by column chromatography (spheric silica; eluent: toluene:MTBE:methanol=5:4:1) to give 4.68 g of the title compound (VIb) (70%) as a yellow solid.

Purity by HPLC: 98.7%.

M.p.: 139-142° C.

^{1}H NMR (DMSO): 7.89 (d, J=8.6 Hz, 2H); 6.80 (d, J=8.5 Hz, 2H); 4.1 (t, J==7.0 Hz, 2H); 2.51 (t, J==7.0 Hz, 2H); 2.37 (t, J=7.0 Hz, 4H); 2.16 (m, 6H); 1.89 (m, 2H); 1.32 (m, 8H); 0.88 (t, J=7.0 Hz, 6H).

Example 7

4-(3-dibutylaminopropoxy)-N-methyl-N-methoxy-benzamide (VIc)

16.25 g of 4-(3-dibutylaminopropoxyl)benzoyl chloride (V) (0.05 mol) and 5.36 g of N,O-dimethyl hydroxylamine hydrochloride (0.055 mol, 1.1 eq) are dissolved in 100 mL of dichloromethane. The reaction mixture is cooled to 0° C. and 9.25 g of pyridine (0.11 mol, 2.2 eq) is added. The mixture is heated to room temperature and it is stirred for 1 hour. The solvent is evaporated in vacuum and 30 mL of brine and 30 mL of dichloromethane are added to the residue. After 15 min stirring the phases are separated and the organic phase is dried on sodium sulfate, the solvent is evaporated and the residue is purified by column chromatography (spheric silica; eluent: toluene:MTBE:methanol=5:4:1) to give 11.9 g of the title compound (VIc) (68%) as a brown solid.

Purity by HPLC: 99.3%.

M.p.: 147-148° C.

^{1}H NMR (DMSO): 7.90 (d, J=8.6 Hz, 2H); 6.86 (d, J=8.6 Hz, 2H); 4.14 (t, J=7.1 Hz, 2H); 3.86 (s, 3H); 2.71 (s, 3H); 2.56 (t, J=7.0 Hz, 2H); 2.39 (t, J=7.0 Hz, 4H); 1.87 (m, 2H); 1.33 (m, 8H); 0.86 (t, J=7.0 Hz, 6H).

Example 8

4-(3-dibutylaminopropoxy)-N,N-diethyl-benzamide (VId)

6.5 g of 4-(3-dibutylaminopropoxyl)benzoyl chloride (V) (0.02 mol) is dissolved in 60 mL of dichloromethane. 1.46 g of diethylamine (0.02 mol, 1 eq) is added and the reaction mixture is cooled to 0° C. 0.43 g TMSCl (0.004 mol, 0.2 eq) is added in 5 min. The reaction mixture is heated to room temperature and stirred for 5 hours. 50 mL of water is added to the mixture, it is stirred for 15 min and the phases are separated. The organic phase is washed with 30 mL of water then it is concentrated. The residue is purified by column chromatography (spheric silica; eluent: toluene:MTBE:methanol=5:4:1) to give 5.58 g of the title compound (VId) (77%) as a yellowish solid.

Purity by HPLC: 98.4%.

M.p.: 151-152° C.

^{1}H NMR (DMSO): 7.89 (d, J=8.6 Hz, 2H); 6.80 (d, J=8.5 Hz, 2H); 4.1 (t, J=7.0 Hz, 2H); 2.51 (t, J=7.0 Hz, 2H); 2.37 (t, J=7.0 Hz, 4H); 2.27 (m, 4H); 2.01 (m, 6H); 1.89 (m, 2H); 1.32 (m, 8H); 0.88 (t, J=7.0 Hz, 6H).

Example 9

4-(3-dibutylaminopropoxy)-N-phenyl-benzamide (VIe)

6.5 g of 4-(3-dibutylaminopropoxyl)benzoyl chloride (V) (0.02 mol) is dissolved in 60 mL of n-hexane. 1.86 g of aniline

(0.02 mol, 1 eq) and 2.76 g of potassium carbonate (0.02 mol, 1 eq) are added. The reaction mixture is heated to 50° C. and stirred for 4 hours. After the reaction the solid inorganic salt is filtered, washed with 2×10 mL of n-hexane and the filtrate is concentrated. The residue is purified by column chromatography (spheric silica; eluent: toluene:MTBE:methanol=5:4:1) to give 6.50 g of the title compound (VIe) (85%) as a yellow solid.

Purity by HPLC: 98.0%.

M.p.: 177-178° C.

^{1}H NMR (DMSO): 7.91 (d, J=8.6 Hz, 2H); 7.74 (br, 1H); 7.51 (d, 2H); 7.26 (m, 3H); 6.86 (d, J=8.6 Hz, 2H); 4.04 (t, J=7.0 Hz, 2H); 2.56 (t, J=7.0 Hz, 2H); 2.39 (t, J=7.0 Hz, 4H); 1.87 (m, 2H); 1.33 (m, 8H); 0.86 (t, J=7.0 Hz, 6H).

Example 10

N-[2-butyl-3-[4-[3-(dibutyl amino)propoxy]benzoyl]-1-benzofuran-5-yl]-methanesulfonamide (I)

6.52 g of N-(2-butyl-3-magnesium-chloro-1-benzofuran-5-yl)methanesulfonamide (IVa) (0.02 mol) in 32 mL of THF (prepared as in Example 3), 6.12 g of 4-(3-dibutylaminopropoxy)benzamide (VIa) (0.02 mol), 0.096 g of $FeCl_3$ (0.6 mmol, 0.03 eq) and 80 mL of THF are added into a flask under nitrogen. The reaction mixture is heated to 35° C. and stirred for 1 hour at this temperature. After the reaction is completed the mixture is cooled to 10° C. and poured into 1 M HCl solution, and the product is extracted with 50 mL of diethyl ether. The organic phase is washed with $NaHCO_3$ solution and evaporated. The product is purified by column chromatography (spheric silica; eluent: toluene:ethyl acetate=7:3) to give 8.80 g of dronedarone (I) (79%).

Purity by HPLC: 99.8%.

^{1}H NMR (DMSO): 7.77 (d, J=8.5 Hz, 2H); 7.27 (m, 3H); 6.91 (d, J=8.5 Hz, 2H); 5.52 (bs, 1H); 4.05 (t, J=6.0 Hz, 2H); 2.87 (s, 3H); 2.78 (t, J=7.0 Hz, 2H); 2.55 (t, J=7.0 Hz, 2H); 2.39 (t, J=7.0 Hz, 4H); 1.90 (m, 2H); 1.70 (m, 2H); 1.3-1.4 (m, 10H); 0.8-0.9 (m, 9H).

Example 11

N-[2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]-1-benzofuran-5-yl]-methanesulfonamide (I)

8.15 g of N-(2-butyl-3-magnesium-chloro-1-benzofuran-5-yl)methanesulfonamide (IVa) (0.025 mol) in 38 mL of THF (prepared as in Example 3), 8.36 g of 4-(3-dibutylaminopropoxy)-N,N-dimethyl-benzamide (VIb) (0.025 mol), 0.12 g of $FeCl_3$ (0.75 mmol, 0.03 eq) and 100 mL of THF are added into a flask under nitrogen. The reaction mixture is heated to 35° C. and stirred for 3 hours at this temperature. After the reaction is completed the mixture is cooled to 10° C. and poured into 1 M HCl solution, and the product is extracted with 60 mL of diethyl ether. The organic phase is washed with $NaHCO_3$ solution and evaporated. The product is purified by column chromatography (spheric silica; eluent: toluene:ethyl acetate=7:3) to give 10.44 g of dronedarone (I) (75%).

Purity by HPLC: 99.6%.

The product is identical with the compound prepared in Example 10.

Example 12

N-[2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]-1-benzofuran-5-yl]-methanesulfonamide (I)

9.26 g of N-(2-butyl-3-magnesium-chloro-1-benzofuran-5-yl)methanesulfonamide (IVb) (0.025 mol) in 40 mL of THF (prepared as in Example 4), 9.06 g of 4-(3-dibutylaminopropoxy)-N,N-diethyl-benzamide (VId) (0.025 mol), 0.12 g of $FeCl_3$ (0.75 mmol, 0.03 eq) and 100 mL of THF are added into a flask under nitrogen. The reaction mixture is heated to 35° C. and stirred for 3 hours at this temperature. After the reaction is completed the mixture is cooled to 10° C. and poured into 1 M HCl solution, and the product is extracted with 60 mL of diethyl ether. The organic phase is washed with $NaHCO_3$ solution and evaporated. The product is purified by column chromatography (spheric silica; eluent: toluene:ethyl acetate=7:3) to give 10.58 g of dronedarone (I) (76%).

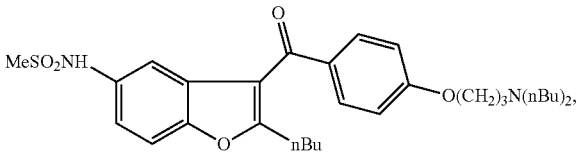
Purity by HPLC: 99.6%.

The product is identical with the compound prepared in Example 10.

The invention claimed is:

1. A process for the preparation of dronedarone (I)

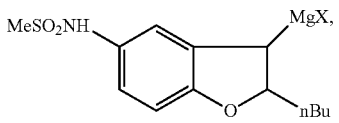
[I]



or a pharmaceutically acceptable salt thereof, comprising the steps of:

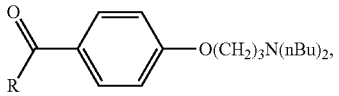
a) reacting a compound of formula (IV)

[IV]



wherein X is Cl or Br, with a compound of formula (VI)

[VI]



or a salt thereof, in a Grignard reaction,

wherein R is a group of formula —NR^1R^2,

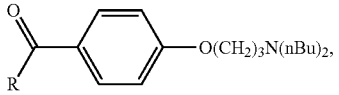
wherein R^1 and R^2 are independently selected from the group consisting of H, alkyl, alkyloxy and aryl;

b) isolating dronedarone (I); and

c) optionally converting dronedarone (I) into a pharmaceutically acceptable salt thereof.

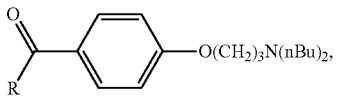
2. A compound of formula (VI),

[VI]



or a salt thereof, wherein R is a group of formula —NR^1R^2, wherein R^1 and R^2 are independently selected from the group consisting of H, alkyl, alkyloxy and aryl.

3. A process for the preparation of the compound of formula (VI))

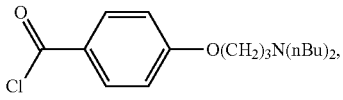


[VI]

or a salt thereof,

comprising the steps of:

a) reacting a compound of formula (V)



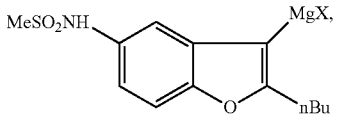
[V]

or a salt thereof, with an amine of formula H—R, or a salt thereof, in a solvent or in a mixture of solvents, wherein R is a group of formula —NR^1R^2, wherein R^1 and R^2 are independently selected from the group consisting of H, alkyl, alkyloxy and aryl;

b) isolating the compound of formula (VI); and

c) optionally converting the compound of formula (VI) into a salt thereof.

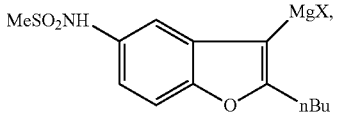
4. A compound of formula (IV)



[IV]

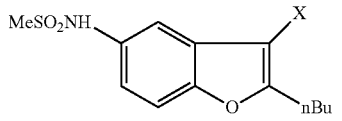
wherein X is Cl or Br.

5. A process for the preparation of the compound of formula (IV)



[IV]

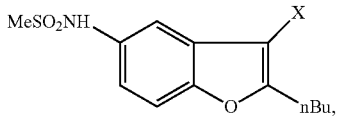
comprising reacting a compound of formula (III)



[III]

with Mg in an anhydrous solvent, wherein X is Cl or Br.

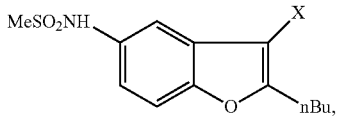
6. A compound of formula (III)



[III]

wherein X is Cl or Br.

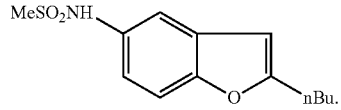
7. A process for the preparation of the compound of formula (III)



[III]

wherein X is Cl or Br,

comprising halogenating a compound of formula (II)

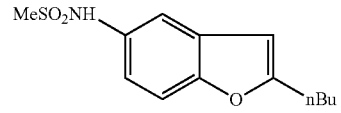


[II]

8. The process

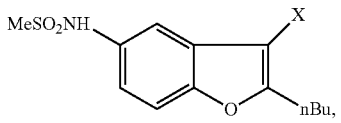
of claim 1 further comprising a process for the preparation of the compound of formula (IV), wherein:

a compound of formula (II)



[II]

is halogenated to obtain a compound of formula (III)



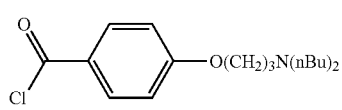
[III]

wherein X is Cl or Br; and

the obtained compound (III) is converted into the compound of formula (IV);

and further comprising a process for the preparation of the compound of formula (VI), wherein:

a compound of formula (V)



[V]

is reacted with an amine of formula H—R, wherein R is as defined in claim 1, to obtain the compound of formula (VI).

9. The process of claim **1**, wherein step a) further comprises an anhydrous solvent and a catalyst.

10. The process of claim **9**, wherein the solvent is THF and the catalyst is $FeCl_3$.

11. The compound of claim **2**, wherein R^1 and R^2 are independently selected from the group consisting of H, methyl, ethyl, methoxy, and phenyl.

12. The process of claim **3**, wherein the solvent is dichloromethane or n-hexane and wherein step a) further comprises a catalyst.

13. The process of claim **3**, wherein the amine is selected from the group consisting of ammonia, dimethylamine, diethylamine, N,O-dimethyl hydroxylamine, and aniline.

14. The compound of claim **4**, wherein X is Cl.

15. The compound of claim **4**, wherein X is Br.

16. The compound of claim **6**, wherein X is Cl.

17. The compound of claim **6**, wherein X is Br.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 9,238,636 B2
APPLICATION NO. : 14/403528
DATED : January 19, 2016
INVENTOR(S) : Csaba Huszár et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page, Item (56):

On page 2, section "FOREIGN PATENT DOCUMENTS", left-hand side column, lines 43-44 of this section: please replace

"WO W0-03/048144 A2 6/2013
WO W0-03/048144 A3 6/2013" with
--WO WO-03/048144 A2 6/2003
WO WO-03/048144 A3 6/2003--;

On page 2, section "OTHER PUBLICATIONS", right-hand side column, line 7 of this column: please replace "ofTosylchymotrypsin" with --of Tosylchymotrypsin--;

On page 2, section "OTHER PUBLICATIONS", right-hand side column, line 11 of this column: please replace "49:45854587" with --49:4585-4587--;

On page 2, section "OTHER PUBLICATIONS", right-hand side column, line 12 of this column: please replace "a,6-Alkynylketones" with --α,β-Alkynylketones--;

On page 2, section "OTHER PUBLICATIONS", right-hand side column, line 14 of this column: please replace "32(48):70917092" with --32(48):7091-7092--;

On page 2, section "OTHER PUBLICATIONS", right-hand side column, line 57 of this column: please replace "Desmethyiated" with --Desmethylated--;

Signed and Sealed this
Fifth Day of July, 2016

Michelle K. Lee

Michelle K. Lee
Director of the United States Patent and Trademark Office

On page 2, section "OTHER PUBLICATIONS", right-hand side column, line 64 of this column: please replace "lnitio" with --Initio--;

On page 2, section "OTHER PUBLICATIONS", right-hand side column, line 71 of this column: please replace "6-Diketones" with --β-Diketones--;

On page 2, section "OTHER PUBLICATIONS", right-hand side column, line 72 of this column: please replace "c-Acylcaproic" with --ε-Acylcaproic--;

On page 3, section "OTHER PUBLICATIONS", left-hand side column, line 18 of this section: please replace "6-Ketoamines" with --β-Ketoamines--;

On page 3, section "OTHER PUBLICATIONS", left-hand side column, line 24 of this section: please replace "El Sevior" with --Elsevier--;

On page 3, section "OTHER PUBLICATIONS", left-hand side column, line 38 of this section: please replace "0-(nitrofenil)-acetofenonoxime" with --O-(nitrofenil)-acetofenonoxime--;

On page 3, section "OTHER PUBLICATIONS", left-hand side column, line 40 of this section: please replace "0-Arilarea" with --O-Arilarea--;

On page 3, section "OTHER PUBLICATIONS", left-hand side column, line 45 of this section: please replace "Wiley lnterscience" with --Wiley Interscience--;

On page 3, section "OTHER PUBLICATIONS", left-hand side column, line 48 of this section: please replace "Wiley lnterscience" with --Wiley Interscience--;

On page 3, section "OTHER PUBLICATIONS", left-hand side column, lines 53-54 of this section: please replace "a-Dialkylamino-w-Methylaminoalkanes" with --α-Dialkylamino-ω-Methylaminoalkanes--;

On page 3, section "OTHER PUBLICATIONS", left-hand side column, line 58 of this column: please replace "20-Hydroxy5,6,11,14-Eicosatetraenoic" with --20-Hydroxy-5,6,11,14-Eicosatetraenoic--;

On page 3, section "OTHER PUBLICATIONS", right-hand side column, line 13 of this column: please replace "Acs" with --ACS--;

On page 3, section "OTHER PUBLICATIONS", right-hand side column, line 18 of this section: please replace "lodoacetic" with --Iodoacetic--;

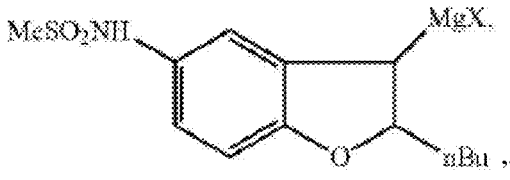
On page 3, section "OTHER PUBLICATIONS", right-hand side column, line 19 of this section: please replace "L-Methionine to L-Homoserine" with --$_{L}$-Methionine to $_{L}$-Homoserine--;

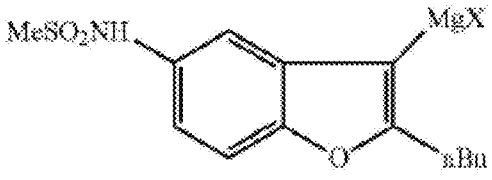
On page 3, section "OTHER PUBLICATIONS", right-hand side column, lines 20-21 of this section: please replace "11 1(4): 1363-1367." with --111(4):1363-1367.--; and

On page 3, section "OTHER PUBLICATIONS", right-hand side column, line 42 of this section: please replace "61:78337863" with --61:7833-7863--.

In the Claims:

At column 12, claim number 1, line number 35: please replace

" 

" with -- 

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